pared with that of nonusers. At present, contraindications for postmenopausal estrogen replacement are personal history of breast cancer, endometrial cancer, or deep venous thrombosis. An adverse effect of estrogen therapy is endometrial hyperstimulation, which can lead to hyperplasia and eventually carcinoma. The relative risk estimates for endometrial cancer associated with estrogen replacement range from 2 to 12, depending on the duration of estrogen use and the cumulative dose. The incidence of endometrial hyperplasia in patients receiving continued unopposed estrogen therapy is 15% to 50%, but this can be reduced to zero if progesterone is added for at least ten days each month. The duration of the progestin treatment each month is more important than the dose in preventing endometrial hyperplasia. The progestational side effects appear to be more dose-dependent and include symptoms like abdominal bloating, headache, depression, and acne. Another serious effect is a reduction in the beneficial effect of estrogen on the HDL cholesterol.

A standard regimen for hormone replacement therapy has been the cyclic administration of estrogen and progestin. A new approach has recently been introduced involving the use of continuous combined treatment. Four studies have looked at the daily use of estrogen—conjugated equine estrogen, 0.625 mg, or estradiol valerate, 2 mg—and a low-dose progestin, such as medroxyprogesterone acetate, 2.5 to 5 mg, or norethindrone, 0.35 to 2 mg, in 148 postmenopausal women observed for 3 to 18 months. These treatments were consistently shown to produce amenorrhea with an inactive endometrium, while alleviating climacteric symptoms. The amount of breakthrough bleeding tended to decrease with the increasing doses of progestin used. Most of the bleeding occurred during the first four months of treatment, and by the ninth month spotting was uncommon regardless of the dose used. It is reassuring that despite breakthrough bleeding, no endometrial hyperplasia was found during continuous treatment in any of the women studied. Two short-term trials using daily conjugated equine estrogen, 0.625 mg, and medroxyprogesterone acetate, 2.5 mg, showed either no change in lipoprotein levels or a statistically significant decrease in total and low-density-lipoprotein cholesterol levels from pretreatment values.

The optimal formulation for daily hormonal therapy in postmenopausal women is still unknown. It seems reasonable to initiate treatment with one of the combinations already studied, like conjugated estrogen plus low-dose medroxyprogesterone acetate. After several months the progestin dose may be adjusted, either downward to the lowest dose that maintains amenorrhea, or upward if breakthrough bleeding occurs. If bleeding persists on a higher dose, it would be prudent to do a gynecologic evaluation and possible endometrial biopsy. If breakthrough bleeding is minimal after a few months of treatment, standard guidelines for routine pelvic examinations and Pap smears could be followed. If larger studies continue to show a complete suppression of endometrial proliferation on continuous combined therapy, there should be no need to do regular endometrial biopsies on these patients. There are many other issues to be considered in the management of perimenopausal women who still have cyclic bleeding, but these will not be discussed here.

In summary, the use of a daily combination of estrogen with a very-low-dose progestin may be an easy, convenient, and safe way to provide hormone replacement in postmenopausal women. This treatment seems preferable to conventional therapy because it avoids cyclic bleeding and reduces progestational side effects while protecting the endometrium. It may also prevent the climacteric symptoms that some women experience during the period of estrogen withdrawal. Larger long-term studies are still needed to document that the benefits of adding continuous low-dose progestin to estrogen replacement outweigh the risks.

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Ganciclovir for Cytomegalovirus Retinitis

RETINITIS IS the most common manifestation of cytomegalovirus (CMV) disease in immunocompromised patients, especially those with the acquired immunodeficiency syndrome (AIDS). Although CMV infection can cause disease at other sites, such as the esophagus, colon, and central nervous system, the retina is the most commonly involved site in patients with AIDS. Although CMV infection is an unusual index AIDS diagnosis, this infection will develop in 5% to 10% of patients at some time during the course of the disease. Lengthened survival due to improved antiretroviral chemotherapy and the suppression of *Pneumocystis carinii* pneumonitis will doubtless increase the incidence of other opportunistic infections such as CMV.

Ganciclovir has recently been approved by the Food and Drug Administration for the treatment of life-threatening CMV retinitis. It is a nucleoside analogue like acyclovir. Clinical trials with ganciclovir began in 1984, and clinicians (especially those caring for AIDS patients) quickly came to the conclusion—in the absence of prospective, comparative studies—that the drug was effective. It was not until several years later, however, that a series of prospective and retrospective clinical trials provided convincing evidence of efficacy.

Ganciclovir is currently recommended for the treatment of sight-threatening CMV retinitis. Patients with this disease have visual symptoms, and retinoscopy shows the typical changes of CMV retinitis—perivascular hemorrhages and whitish "exudates" (actually, necrotic retinal tissue). Asymptomatic patients with rapidly progressive retinitis moving toward the macula may also warrant treatment. Therapy for patients with asymptomatic, nonprogressive or slowly progressive peripheral CMV retinitis or those with end-stage (blinding) retinitis in one eye is still controversial. It is not yet clear that the benefits of long-term ganciclovir therapy exceed the risks of toxicity in such patients.

Treatment with ganciclovir is traditionally divided into two phases: the initial treatment phase—usually called the "induction" phase, by analogy with cancer chemotherapy—and the later phase of long-term chemosuppression, usually called the "maintenance" phase. The drug is always given intravenously. The induction dose is 5 mg per kg of body weight given every 12 hours for 14 days; the dose needs to be reduced for patients with renal insufficiency. All patients receiving induction should be placed on a maintenance

dose of the drug, the risk of relapse being virtually 100% for those not treated; most experts recommend 5 to 6 mg per kg a day, given once daily five to seven days per week. Both the latter part of the induction phase and the maintenance phase can be given at home. Patients should be monitored fortnightly by an ophthalmologist.

The principal toxic effect of ganciclovir is neutropenia. Dose-limiting neutropenia will develop in about 10% of patients during induction and in 20% during the maintenance phase. We recommend discontinuing therapy if the absolute neutrophil count falls to 500×10^6 per liter. After the granulocyte count returns to baseline, many patients can tolerate a reduced dose. Synergistic toxicity with zidovudine (AZT) is nearly universal, and only a small proportion of patients will be able to tolerate even reduced doses of AZT with maintenance ganciclovir. Other adverse effects, such as thrombocytopenia, hepatitis, eosinophilia, nausea and vomiting, confusion, and rash, are less common and are rarely dose limiting.

As the first drug effective against CMV disease, ganciclovir is a major therapeutic breakthrough, but it is toxic, dose-limiting adverse reactions are common, and it must be given by intravenous infusion. Therapy with this drug should therefore be reserved for patients with sight-threatening CMV retinitis.

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Monitoring Sodium Warfarin Therapy Using the International Normalized Ratio

THE PROTHROMBIN TIME (or prothrombin ratio), the time-honored test used to monitor the anticoagulant effect of sodium warfarin therapy, is gradually being supplemented or replaced by a new measure, the international normalized ratio (INR). The use of the INR is being adopted because the thromboplastin reagents used in different laboratories to measure the prothrombin time may have significantly different sensitivities to warfarin-induced changes in vitamin K-dependent clotting factors. The prothrombin time results from two different laboratories on a single specimen of plasma may show a difference in the measurement as great as two to three seconds! Thus, a patient who has an apparently "therapeutic" prothrombin time measurement in one laboratory may have a nontherapeutic prothrombin time result in a different laboratory.

Conceptually, the INR standardizes prothrombin time measurements by taking into account the sensitivity of the thromboplastin reagent being used. Mathematically, the $INR = (PR)^{ISI}$, where the PR is the prothrombin ratio—a patient's prothrombin time divided by the control prothrombin time—and the exponent is the international sensitivity index (ISI) of the reagent. Thus, the INR is identical to the prothrombin ratio when the ISI is 1.0. In Great Britain, where human brain thromboplastins are used, the ISI values are close to 1.0, but in the United States, where rabbit brain thromboplastins are used, ISI values are notably higher, in the range of 1.9 to 2.6.

Recently published guidelines for managing oral anticoagulant therapy define optimal therapeutic target ranges using INR units. Most thromboembolic disorders can be successfully treated using "low-intensity" oral anticoagulation therapy, with the INR between 2.0 and 3.0. These conditions include the treatment of deep vein thrombosis and pulmonary embolism; the prevention of venous thromboembolism in patients undergoing a high-risk surgical procedure; and the prevention of systemic embolization in patients with tissue heart valves, valvular heart disease, atrial fibrillation, and after an acute myocardial infarction. "High-intensity" anticoagulation therapy, with the INR between 3.0 and 4.5, is necessary to prevent systemic embolization in patients who have a mechanical prosthetic heart valve and to treat patients who have a thromboembolic complication while on low-intensity therapy.

If a clinical laboratory does not provide the INR value with each prothrombin time, it is possible to determine it by requesting the ISI value of the thromboplastin reagent and finding the INR value on a published nomogram. (The INR value can also be easily calculated using a pocket calculator equipped with logarithmic and exponential functions.) If the ISI of the thromboplastin reagent is unknown, there is no way to calculate the INR value. Assuming that a thromboplastin reagent has an ISI value of 2.4 and that the control prothrombin time is 12 seconds, the low-intensity INR range of 2.0 to 3.0 is equivalent to a prothrombin time between 16 and 19 seconds, and the high-intensity INR target range of 3.0 to 4.5 is equivalent to a prothrombin time between 19 and 22.5 seconds.

The widespread use of the INR will allow a direct comparison of results from different clinical laboratories, but it will undoubtedly take time for clinicians to become familiar with INR units, particularly the fact that for any change in a patient's coagulation status, the INR will change more than the prothrombin time. For example, if the ISI of a thromboplastin reagent is 2.4, an increase in the prothrombin time from 18 to 24 seconds more than doubles the INR value, which rises from 2.6 to 5.2. Although using the INR will require some adjustment, it is certainly a step in the right direction of achieving better control of anticoagulation therapy.

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Medical Treatment of Breast Cancer

THE MANAGEMENT OF carcinoma of the breast has been under intense review for the past decade and has been the source of several well-constructed, multi-institutional clinical trials. As data from these trials have matured, they have changed the practice of cancer management.

Recently eight-year follow-up data have been presented